Master's Thesis

Synthesis and application of fluorinated ethers, baicalein and quinazolinone derivatives.

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Approved by

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Advisor
Prof. Sung You Hong

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12. 13. 2018 of submission

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Prof. Nam–Soon Choi: Thesis Committee Member #2

Abstract

Organofluorine chemistry plays an essential role in pharmaceuticals, agrochemicals and material fields. Owing to the high electronegativity of fluorine atom, the introduction of fluorine into organic molecule affects the properties. Therefore, many researchers are having large interest on fluorination chemistry and in particular, the introduction of trifluoromethyl group have been remained formidable challenges. While trifluoromethylation of hetereoarenes have made remarkable progress, *O*–trifluoromethylation of alcohols are still underdeveloped. According to the Qing group, reported in 2015, they have demonstrated efficient and practical method to achieve *O*–trifluoromethylation of various alcohols. Based on the Qing group's report, herein, we synthesized a few substrates of partially fluorinated ether compounds. Besides, we also tested those ethereal compounds as Li–metal battery additives with assistance from Prof. Nam–Soon Choi group.

Due to the inherent limitations of Li–ion batteries, the development of post-energy-storage systems is widely investigated. Li–metal is considered as next generation of Li-based battery because it has the highest theoretical capacity and low electrochemical potential. Nevertheless, it has not been commercialized on account of safety and cycle durability issues. Thus, a lot of researchers strive for suppressing Li dendrite growth by controlling electrolyte or Li anode and additive is one of the choices. Fluoroethylene carbonate (FEC) is one of the representative electrolyte additives in Li–ion batteries, however, unlike Li–ion system, carbonate-based additives are not the best choice. Instead, ethers are better electrolyte solvents that show higher Coulombic efficiency and evident dendrite suppression. We also found papers about the use of quercetin as electrolyte additive in Li–ion batteries. Inspired by the reports and the need of ether bonds in organic molecules for the proper additive, we prepared some baicalein derivatives bearing fluorine sources. They were also tested as Li–metal battery additives with assistance from Prof. Nam–Soon Choi group.

Trifluoroethylated compounds are having great attention because of the biological activities. Introduction of trifluoroethyl group with hypervalent iodonium salts are considered as promising method due to the electrophilicity, nontoxicity and ease of handling. Quinazolinone derivatives can be found in natural products. Owing to the functional groups in the structure, they have been investigated as attractive structural scaffold and many methodologies have constructed. Herein, we report metal-free site-selective *O*–trifluoroethylation of various quinazolinone derivatives with hypervalent iodonium salt under the mild condition.

Contents

List of figures

Figure S2.8. ^{1}H NMR (400 MHz, $CDCl_3$) of the compound **I-3_CF$_3$**

Figure S2.9. ^{19}F NMR (376 MHz, $CDCl_3$) of the compound **I-3_CF$_3$**

Figure S2.10. ^{1}H NMR (400 MHz, $CDCl_3$) of the compound **I-4_CF$_3$**

Figure S2.11. ^{19}F NMR (376 MHz, $CDCl_3$) of the compound **I-4_CF$_3$**

Figure S2.12. ^{1}H NMR (400 MHz, $CDCl_3$) of the compound **I-3_OCF$_3$**

Figure S2.13. ^{19}F NMR (376 MHz, $CDCl_3$) of the compound **I-3_OCF$_3$**

Figure S2.14. ^{1}H NMR (400 MHz, $CDCl_3$) of the compound **I-4_OCF$_3$**

Figure S2.15. ^{19}F NMR (376 MHz, $CDCl_3$) of the compound **I-4_OCF$_3$**

Figure 3.1. A representative iodonium salt for 2,2,2-trifluoroethylation

Figure 3.2. Quinazolinone and representative derivatives found in natural products

List of tables

List of schemes

Abbreviation

SEI	Solid electrolyte interphase
$TMSCF_3$	Trifluoromethyl trimethylsilane
AgOTf	Silver trifluoromethanesulfonate
EtOAc	Ethyl acetate
KF	Potassium fluoride
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
LiFSI	Lithium bis(fluorosulfonyl)imine
DME	1,2-dimethoxyethane
GC-MS	Gas chromatography–mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
FEC	Fluoroethylene carbonate
J	Coupling constants
Hz	Hertz
TLC	Thin layer chromatography
NaH	Sodium hydride
THF	Tetrahydrofuran
Et_2O	Diethyl ether
TBAB	Tetrabutylammonium bromide
Ar	Argon
LIB	Lithium ion battery
ICE	Initial Coulombic efficiency
CE	Coulombic efficiency
NaOAc	Sodium acetate
Ac_2O	Acetic anhydride
$BF_3{\cdot}OEt_2$	Boron trifluoride diethyl etherate
AcOH	Acetic acid
KOH	Potassium hydroxide

EtOH	Ethanol
I_2	Iodine
DMSO	Dimethyl sulfoxide
KI	Potassium iodide
K_2CO_3	Potassium carbonate
MeCN	Acetonitrile
N_2	Nitrogen
LC–MS	Liquid chromatography–mass spectrometry
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulfate
HCl	Hydrochloric acid
NH_4Cl	Ammonium chloride
HRMS	High-resolution mass spectrometry

Chapter I

Synthesis and application of trifluorinated ethers through *O*–trifluoromethylation for Li–metal battery additives

Collaboration: All the electrochemical analyses of JS–series were done by Yongwon Lee (Prof. Nam–Soon Choi group)

1. Introduction

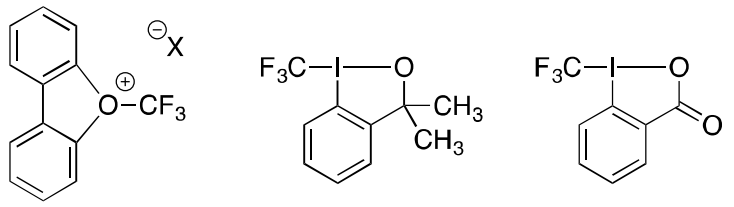
Organofluorine chemistry which began to develop more than a century ago, is still having significant challenges. Current interests in fluorine chemistry are pharmaceutical-, agrochemical-, and battery industries by introducing fluorine to the molecule. In fact, half of the top ten selling medicines in 2005 were fluorinated molecules and approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine atoms.[1-3]

Fluorinated organic compounds, especially ether, have been used as a solvent, co-solvent and additive to enhance the Li-based battery electrolyte performance. Fluoroethylene carbonate is the representative fluorinated electrolyte additive for Li-ion batteries, however, the inherent limitations of Li-ion chemistry and growing demand for higher energy capacity require beyond current technologies. Instead. lithium-metal is considered as the best option for Li^0 anode in rechargeable batteries. Unlike lithium-ion batteries, organic carbonate additives are not the best choice for lithium-metal cells because of the formation of rigid solid electrolyte interphase (SEI) layer. Ethers show higher Coulombic efficiency (>98%) and apparent Li dendrite suppression effect in many systems, however, as a result of high flammability and low anodic decomposition voltage, ethers have not been preferred.[7-9] Therefore, it is necessary to develop novel fluorinated ethereal additives for Li-metal batteries.

Recently, there have been extensive efforts contributed to the synthesis of trifluoromethylated compounds. Since the trifluoromethyl group (CF_3) is strongly electron withdrawing substituent, it increases the lipophilicity of molecules, therefore, there are substantial attractions in developing methods for the formation of trifluoromethylated small molecules, especially in pharmaceutical area. However, compared to the significant progress of fluorination methods, trifluoromethylation has been limited and has fewer synthetic strategies.[1,5] Trifluoromethoxylation to organic compounds is the most attractive and simple way to synthesize the ether molecules, however, treating trifluoromethoxy group is very challenging due to poor nucleophilicity, stability and decomposition to carbonyl difluoride.

Transition metal-catalyzed reaction also have a severe problem with formation of carbonyl difluoride and metal fluoride. Instead, many researchers have been investigated the direct trifluoromethylation of alcohols. Nevertheless, the formation of O–CF_3 bond from alcohol is difficult because of the difficulty of orbital overlap with oxygen and carbon, and strong electronic repulsion between oxygen and fluorine which results in the formation of alkoxy halide. For that reason, conventional S_N2 reaction does not work for *O*-trifluoromethylation.[10]

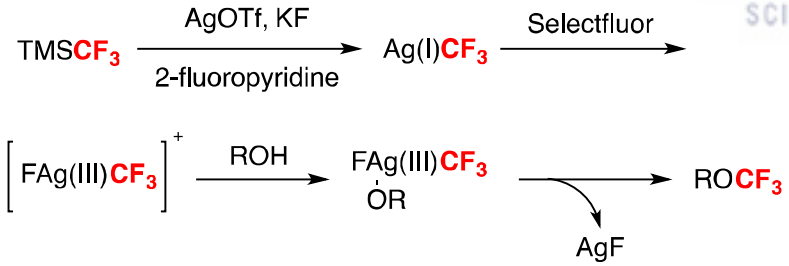
Many research groups reported electrophilic *O*-trifluoromethylation of alcohols using transition metals. In 2007, Umemoto et al. reported the direct electrophilic trifluoromethylation of alcohols, phenols, amines, pyridines and sulfonates using *O*-(trifluoromethyl)dibenzofuranium salts (**1**). However, the electrophilic CF_3 sources used are so much unstable and highly reactive. Recently, the Togni group developed a new synthetic strategy of electrophilic trifluoromethylation based on the hypervalent iodine(III) derivatives (**2**, 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, and **3**, 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one; Figure 1.1). In 2009, the Togni and the zinc-mediated direct *O*-trifluoromethylation of alcohols to ethers with Togni II reagent. In order to obtain good yields, it is necessary to use the alcohol as both the substrate and solvent. However, the conversions of the starting materials were poor owing to the excess amount of alcohols and the use of co–solvent showed even less yield.[3-4,6] Therefore, the development of efficient and practical pathway of direct trifluoromethylation of alcohols to ethers is highly required.



1 **2** **3**

Figure 1.1. Novel electrophilic trifluoromethylating reagents

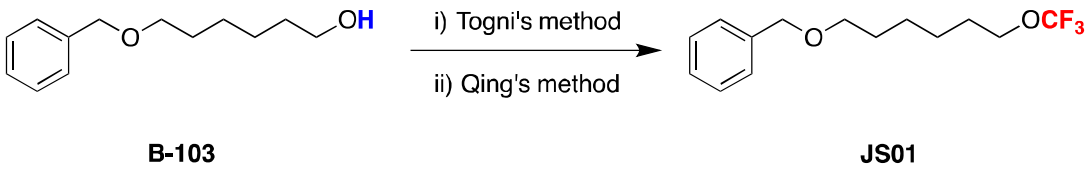
In 2015, the Qing's group reported a silver-mediated oxidative trifluoromethylation of alcohols to trifluoromethyl ethers with the Ruppert–Prakash reagent ($TMSCF_3$).[5] They showed various primary, secondary and tertiary alcohols' trifluoromethylation with moderate to excellent yield under room temperature and inert conditions. They proposed the mechanism that *in situ* generation of trifluoromethyl silver complex, not alkoxy silver complex, and after oxidation step by Selectfluor from Ag(I) to Ag(III), reductive elimination occurs and obtained the desired product (Scheme 1.1). On the basis of the Qing's report, herein we report the formation of trifluoromethyl alkyl ethers and the applications of compounds as Li-metal anode electrolyte additives.



Scheme 1.1. Proposed mechanism of trifluoromethylation by the Qing group

2. Results and Discussions

Initially, 6-benzyloxy-1-hexanol (**B-103**) was tested with the Togni and Qing group's report as a model reaction (Scheme 1.2). For the Togni's condition, owing to the oil form of B-103, it had difficulties of solely used as solvent. Therefore, co–solvent, $CDCl_3$, was needed, however, the conversion showed extremely low and expensive electrophilic CF_3 source reagent hampered further investigation. Instead, our group used the Qing's method with $TMSCF_3$ reagent.

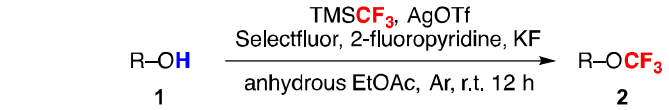


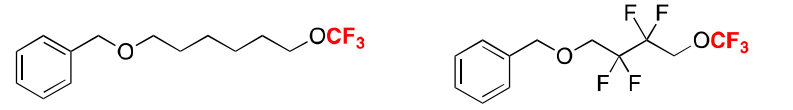
B-103 **JS01**

Scheme 1.2. Two possible synthetic strategies of direct *O*-trifluoromethylation

Through silver-mediated oxidative trifluoromethylation, it led to the formation of 6-benzyloxy-1-trifluoromethoxyhexane (**JS01)** to 63 %. As the model reaction showed moderate yield, few partially fluorinated alcohol derivatives were synthesized (Scheme S1.1). Unexpectedly, fluorinated alcohols did not undergo through *O*–trifluoromethylation more than 50% of yields (Table 1.1). The main problem of the reactions was the low conversion of alcohols. Temperature and time effects were examined, but the condition differences did not show any improvements.

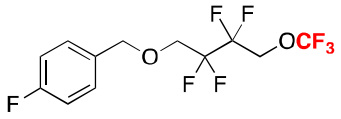
Table 1.1. Substrate scope of trifluoromethyl alkyl ethers



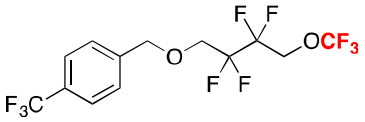


JS01, 63%

JS02, 47%



JS09, 18%

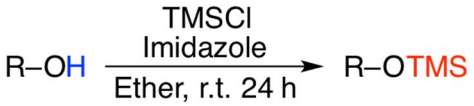


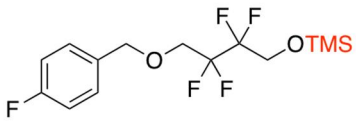
JS12, 26%

[a] Reaction conditions: R–OH (1 equiv.), $TMSCF_3$ (3 equiv.), AgOTf (3 equiv.), Selectfluor (1.5 equiv.), 2-fluoropyridine (3 equiv.), KF (4 equiv.), anhydrous EtOAc (2.5 mL), Ar atmosphere, r.t. 12 h; Isolated yield.

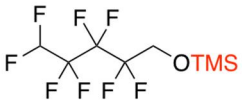
Then, trimethylsilyl alkyl ether compounds were synthesized that are known as efficient additives for fluorinated electrolytes (Table1.2).

Table 1.2. Synthesis of trimethylsilyl alkyl ethers





JS10



JS11

Condition: R–OH (1 equiv), TMSCl (1.5 equiv), Imidazole (2.5 equiv), Ether (30 mL), 0 °C to r.t. 24 h.

Since the role of additives is the formation of stable SEI layer and maintenance of electrolyte, lower LUMO energy levels of additives are certainly required than the electrolyte. All of the candidates showed lower LUMO value than 1,2-dimethoxyethane (DME), thus, Li/Cu cell cycle life tests were conducted (Figure 1.2).

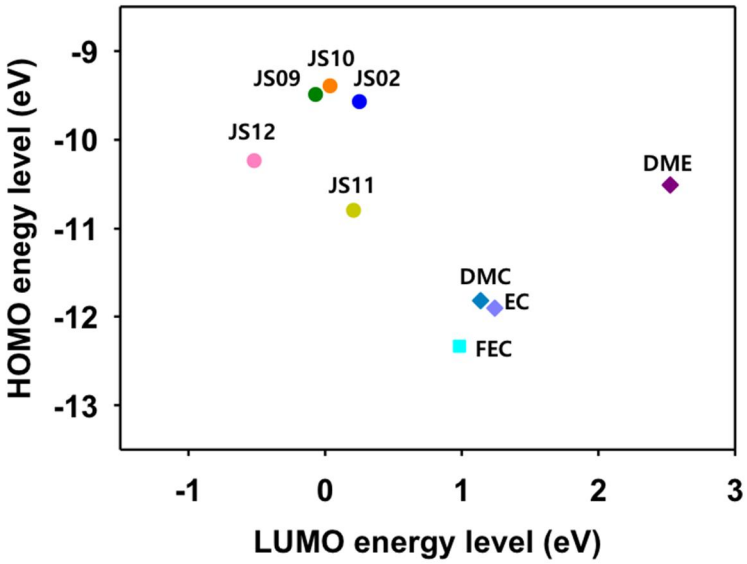


Figure 1.2. HOMO and LUMO levels of electrolyte additive candidates

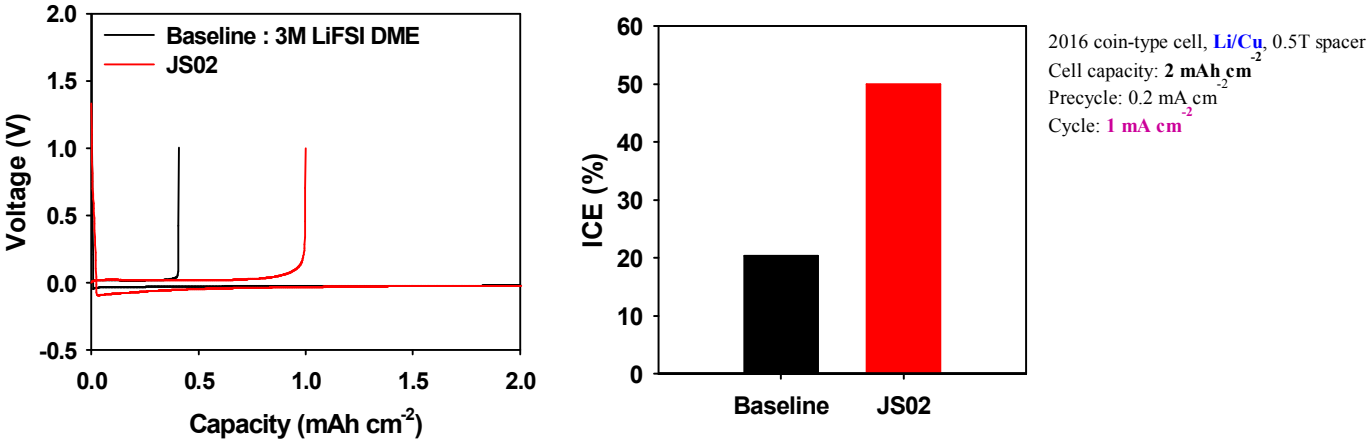


Figure 1.3. Initial coulombic efficiency data after the pre-cycle

Prior to battery cycle, pre-cycle was carried out for the formation of uniform SEI (Figure 1.3) and initial coulombic efficiency of JS02 added electrolyte showed distinct improvement compared to the baseline. Furthermore, coulombic efficiency of JS02 added cell maintains consistently until 350 cycles whereas the baseline began to fluctuate from 200 cycles (Figure 1.4).

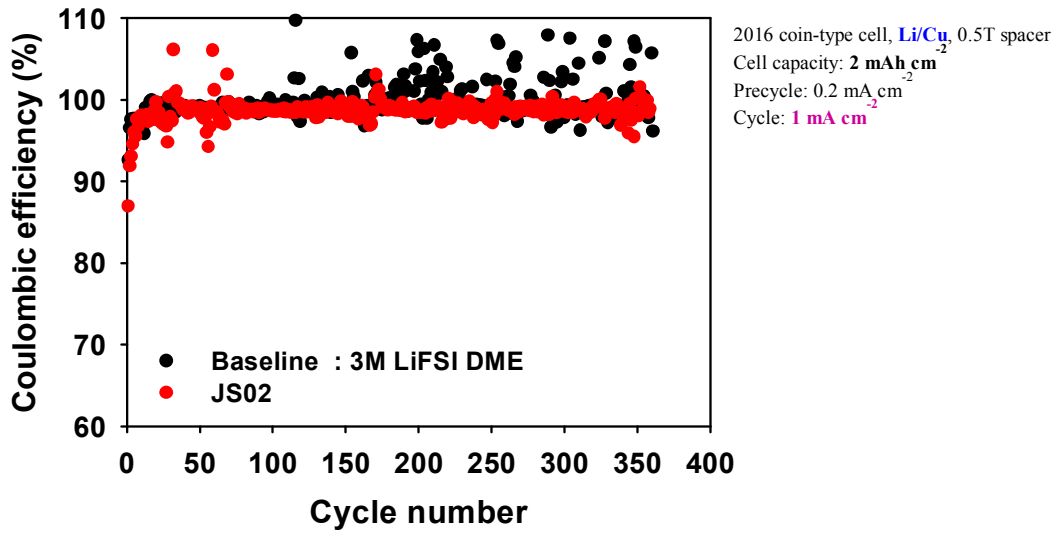


Figure 1.4. Li/Cu cell cycle life test of JS02 added electrolyte

3. Conclusion

In summary, partially fluorinated ethereal compounds were synthesized as Li–metal battery additive candidates. To confirm the additive candidates, ^{1}H, ^{19}F NMR and GC–MS was used. The compound, JS02, showed initial coulombic efficiency and improved cycle life than standard condition. However, due to the low initial coulombic efficiency, it is required to add another additive, such as FEC. We expect the use of JS09 or JS12 could improve more than JS02 owing to the additional fluorine sources. Furthermore, we are also planning to design a trifluoromethoxy group installed partially ethereal compound and test as Li–metal battery additive.

4. References

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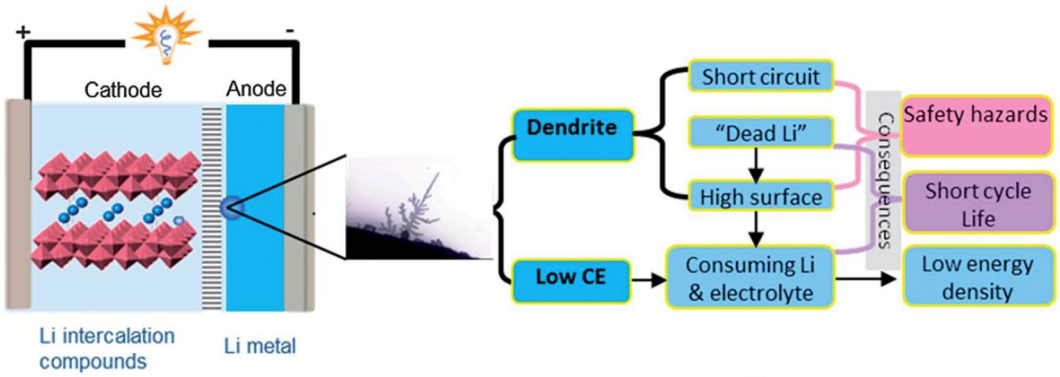
Chapter II

Synthesis and application of baicalein derivatives for Li–metal battery additives

Collaboration: All the electrochemical analyses of I–series were done by Yongwon Lee (Prof. Nam–Soon Choi group)

1. Introduction

Since the pioneer of commercial secondary Li–ion batteries (LIBs) by SONY in 1991, we have observed huge industrial advance in portable electronic devices such as cell phones, laptops and electric vehicles.[a,b] However, in spite of the impressive progress in LIBs owing to the inherent limitation, energy density in particular, the development of post-LIBs is highly demanded.[1,3] Li–metal is deemed the ultimate choice for the next-generation anode material because it has the highest theoretical capacity (3860 mAh g^{-1}), lowest electrochemical potential (-3.040 V vs. standard hydrogen electrode) and lower density (0.534 g cm^{-1}) than graphite.[1–6] However, due to the safety and cyclability issues, it still has not been commercialized (Figure 2.1). Li tends to deposit as dendrite form during **Figure 2.1**.



Schematic diagram of Li metal batteries and the typical morphology of Li dendrites[g]

charging/discharging processes which leads to thermal runaway and a risk of explosion. Low Coulombic efficiency (CE) is another big issue. Simple approach to resolve CE problem is to add excess amount of Li metal, however, the following formation of Li dendrites leads to battery failure and safety problems again.[1,3,7]

Recently, there have been many efforts to understand Li–metal chemistry and Li anode. One of the solutions is combining an additive with electrolyte to modify the physio-chemical properties of solid electrolyte interphase (SEI) so that controlling the formation of Li dendrites. Unlike Li–ion batteries, ethers are much suitable for Li–metal anode systems than organic carbonates. They show higher CE and affect dendrite suppression, however, owing to the low anodic decomposition (<4 V vs Li^+/Li) and high flammability, that have been disregarded from most commercial batteries.[1] Therefore, it is desired to develop a novel types of additives for Li–metal battery systems.

Flavonoids, a group of naturally occurring polyphenolic compounds in many plants, have attracted increasing interest due to their various biochemical and pharmacological properties. Baicalein, from the roots of *Scutellaria baicalensis* Georgi (Huang Qui), is one of the representative flavonoids which exhibit anti-oxidant, neuroprotective effects, anti-inflammatory effects *in vitro* as well as *in vivo* (Figure 2.2).[8-11]

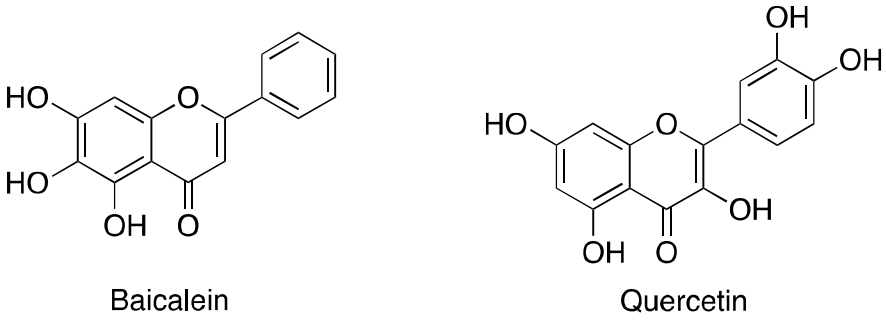


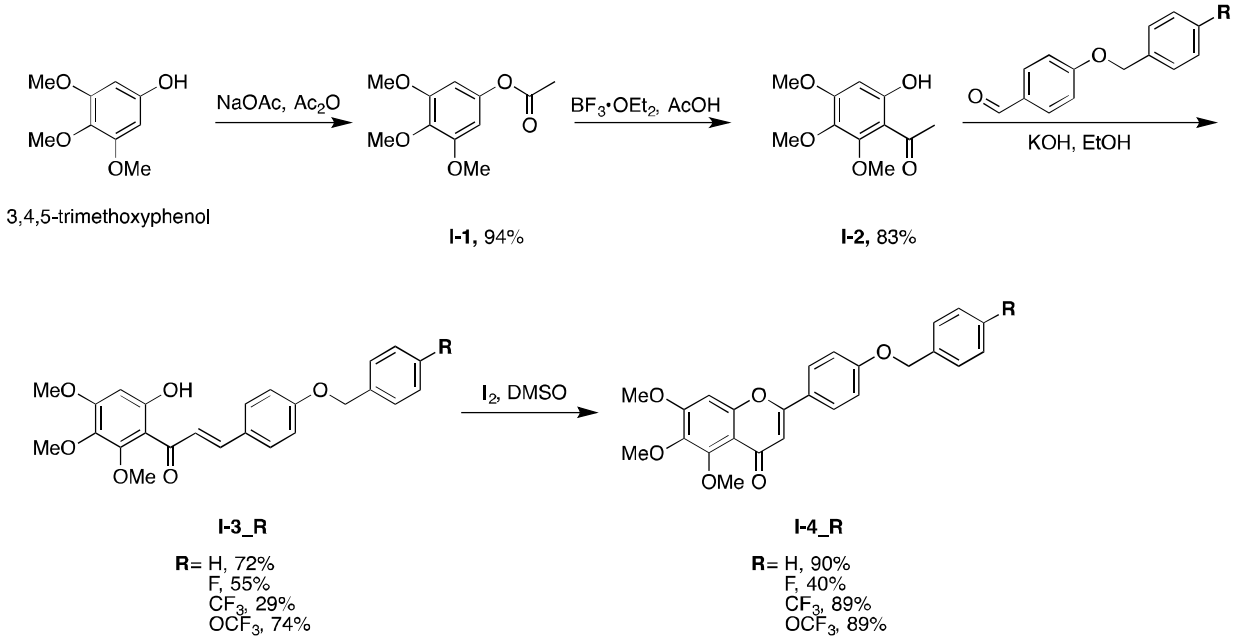
Figure 2.2. The structure of baicalein and quercetin

Surprisingly, there are few reports of quercetin, one of natural flavonoids that show antioxidant property, as electrolyte additive in Li–ion batteries. In 2012, M.–L. Lee *et al.* reported the significant improvement of safety and cycle life of Li–ion batteries by using quercetin as an electrolyte additive.[13] Also, in 2016, S. Kim *et al.* showed the stability of $LiNi_{0.5}Mn_{1.5}O_4$ under high voltage at elevated temperature in the presence of quercetin.[14]

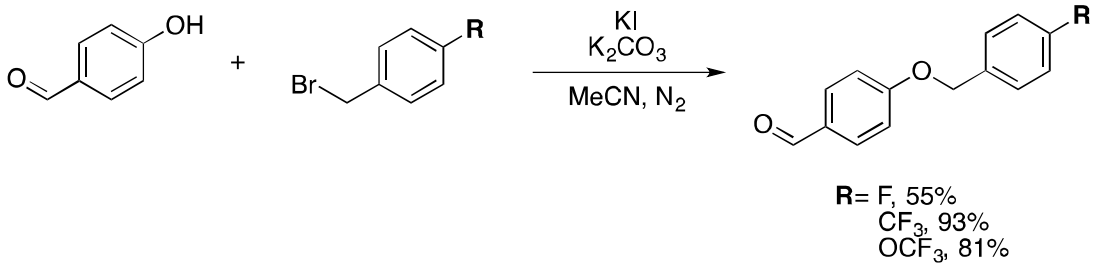
Inspired by the reports of using quercetin, one of the flavonoid derivatives, as Li–ion battery additive, we applied baicalein derivatives that contain ether functional groups as Li–metal battery additives. To compare the performance of additive candidate, fluorinated additives were also synthesized and applicated to Li–metal battery.

2. Results and Discussions

Synthetic approaches for I-4 series are shown in Scheme 2.1. In order to synthesize I-4, acetylation, Fries-rearrangement, aldol condensation and ring-closing reaction were conducted. To synthesize substituted I-4, it is necessary to prepare substituted benzaldehydes and they were attached to I-2 through aldol condensation. Substituted benzaldehydes were prepared according to the reported method (Scheme 2.2).[12] Except 4-fluorobenzylbenzaldehyde (R = F) with moderate yield, CF_3 and OCF_3 substituted benzaldehyde showed good to excellent yields under inert condition. In the case of overall scheme, most of reactions showed good yields, however, I-3_CF_3 and I-4_F showed poor to moderated yields. This is due to the remaining of starting material and reactant under the standard reaction conditions and difficulty of separations. The final products were decolorized with activated carbon after the purification.



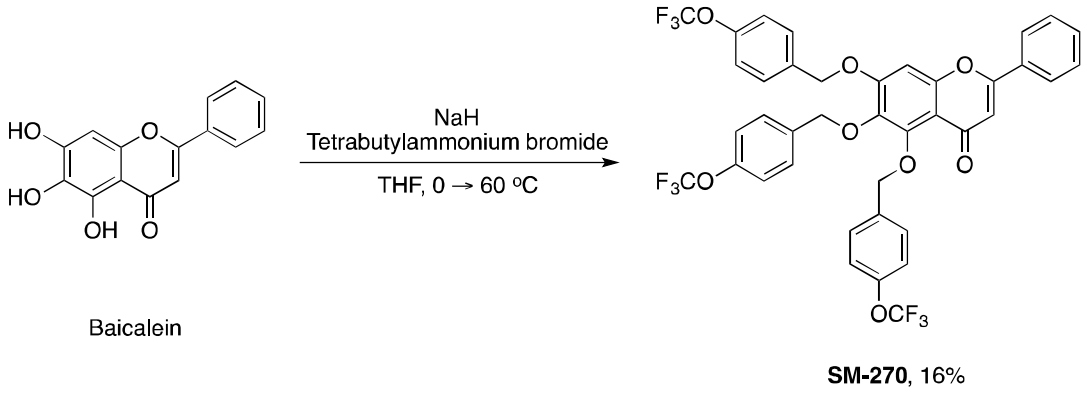
Scheme 2.1. Overall scheme of I-4 series synthesis



Scheme 2.2. Synthesis of substituted benzaldehyde

Furthermore, we designed another type of baicalein derivative that contains a specific functional group on three sites (Scheme 2.3). Due to the presence of trifluoromethoxy group and ether bonds, it is

expected to show good performance and appropriate additive for Li–metal battery. However, the yield of SM-270 turned out to be very poor even with the elevated temperature and longer reaction time. Therefore, it is necessary to optimize condition to obtain higher yield with efficient way in the near future.



Baicalein

SM-270, 16%

Scheme 2.3. Synthesis of SM-270

Then, all of additive candidates were tested for the use of Li–metal battery additives. Prior to proceed the test, HOMO and LUMO values of all candidates were calculated (Figure 2.3). To play role of an additive, it is required to have lower LUMO energy than electrolyte (1,2-dimethoxyethane, DME) for reductive cleavage ahead of DME on anode and higher HOMO energy for oxidative cleavage ahead of DME on cathode. As it is shown in Figure 2.3, all candidates appear to fulfil the requirements, thus battery cycle life tests were conducted.

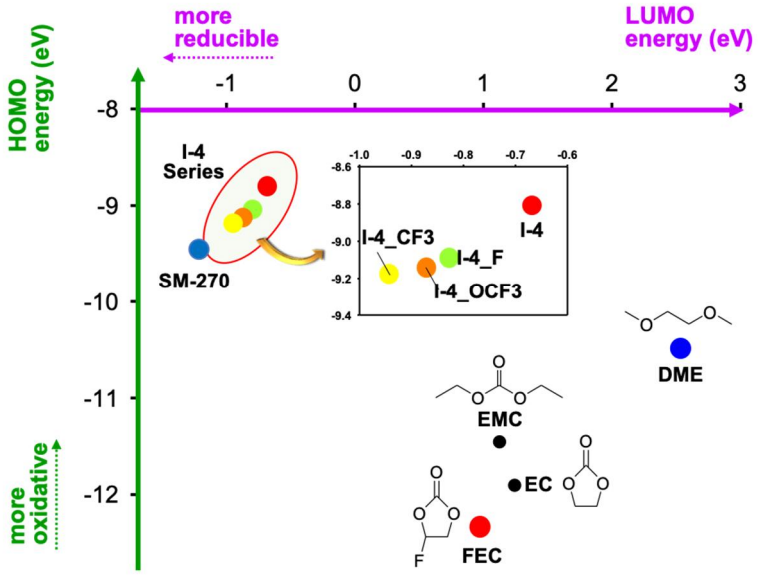
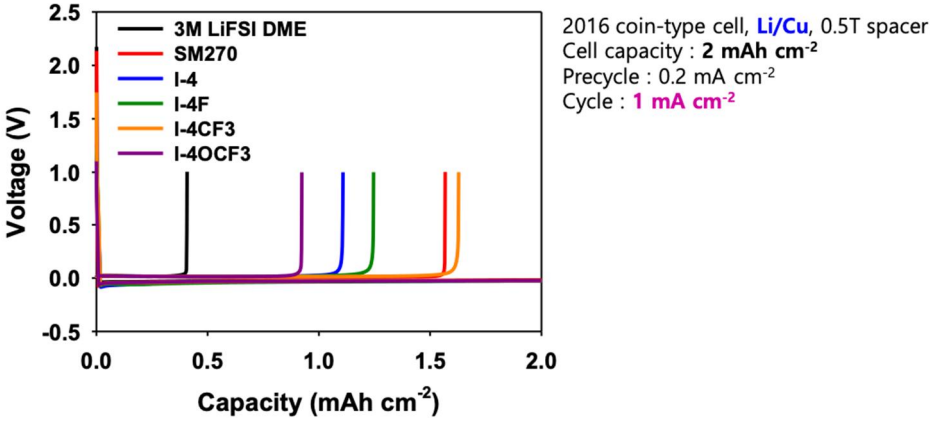


Figure 2.3. HOMO and LUMO energy level of additive candidates

For the formation of a uniform SEI layer, pre-cycle was carried out and initial Coulombic efficiencies (ICE) of each candidate were calculated (Figure 2.4). The pre-cycle value of standard condition (3 M LiFSI DME) turned out extremely low, 20%, whereas additive combined conditions showed up to 81% of ICE. To be a powerful additive, it needs to show ICE up to 90%, however, all the candidates are showing less than 90%. Therefore, it is needed to find the optimal condition of combining I-4 series and fluoroethylene carbonate (FEC) to raise ICE.



	ICE (%)
3M LiFSI DME	20
SM270	65
I-4	55
I-4_F	62
I-4_CF3	81
I-4_OCF3	46

Figure 2.4. ICE values of additive candidates for pre-cycle

After the pre-cycle, battery cycle life tests were conducted to see the effect of additives on electrolyte (Figure 2.5). With 1 wt.% of additives, we could see the cycle life variations. We initially expected the tendency of cycle life would correspond to the ICE values. However, SM-270 appeared the exceptional stability of Coulombic efficiency until 500 cycles as well as I-4. I-4_CF_3 added cell which showed the highest ICE compared to the others began to fail around 150 cycles and I-4_F failed before 100 cycles. In addition, I-4_OCF_3 added cell is under experiment. As it was mentioned above, all candidates should be combined with FEC. Refer to the Figure 2.5, combination of FEC and SM-270 or I-4 candidates are appeared to have influential possibility as promising Li–metal battery additives.

Finally, it is necessary to proceed further analysis to reveal the reasons of unconformity between ICE and CE. Through additional investigation, we believe that the correlation between ICEs and cycle life of battery cells can be comprehended in depth and this might help us to design proper additive materials.

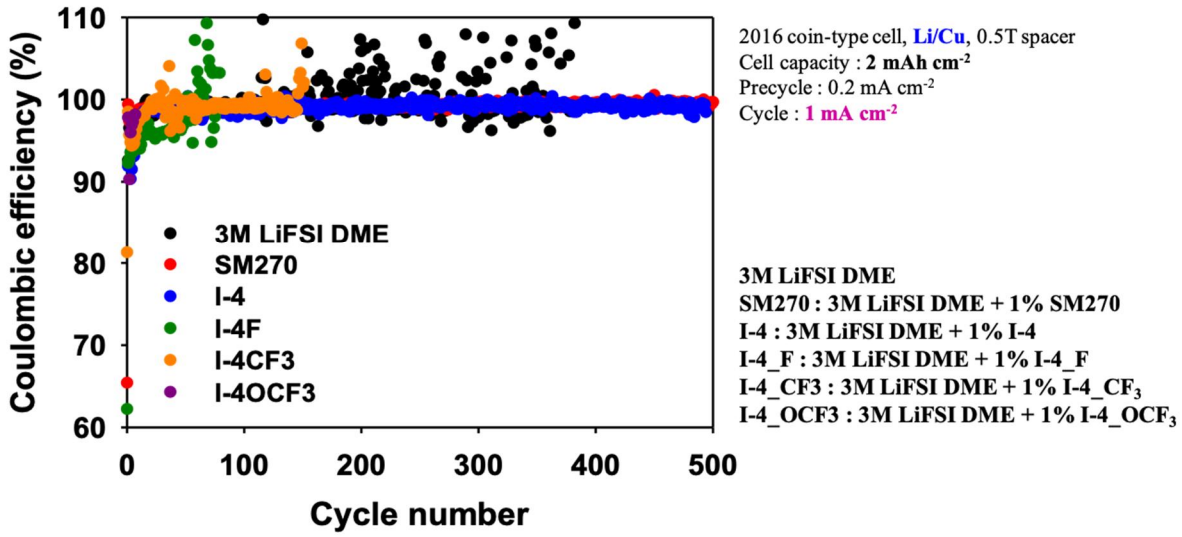


Figure 2.5. Cycle life tests of additive included cells

3. Conclusion

In summary, we have synthesized a few derivatives of baicalein molecules, I-4 series and SM-270 for the use as Li–metal battery additives. To confirm the organic molecules, ^{1}H, ^{19}F NMR and LC–MS was used. All additive candidates were tested for Li/Cu coin-type cell. Among five candidates, I-4_CF_3 showed highest initial Coulombic efficiency with 81% during the pre-cycle, however it could not maintain its Coulombic efficiency more than 200 cycles. Since the initial Coulombic efficiencies of all candidates did not exhibit over 90%, it is recommended to combine with another organic additive material, such as fluoroethylene carbonate (FEC). Compared to the additive-free standard condition which showed stable Coulombic efficiency up to 200 cycles, only SM-270 and I-4 contained cells displayed remarkable stability of Coulombic efficiencies and cycle life. Therefore, further investigations of combined FEC and SM-270, or I-4, will be conducted.

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Chapter III

Late-stage metal-free *O*–trifluoroethylation of Quinazolinone derivatives

1. Introduction

Fluorine-containing organic molecules have been applied to pharmaceutical and agrochemical fields because the presence of fluorine modifies the electronic property, metabolically stable, bioavailable and lipophilic.[1,2] In the past decade, formation of C–C bond through direct trifluoromethylation of heteroarenes have been widely explored whereas installation of CF_3 group bearing alkyl groups are underdeveloped for many reasons such as the poor tendency of alkyl electrophiles to be involved in the classical transition-metal-catalyzed pathways and pre-functionalization of substrates in many cases.[1, 3–6] Among a number of fluorine-containing alkyl groups, trifluoroethylated compounds are having great attention due to the biological activities.

The introduction of trifluoroethyl group through traditional cross-coupling reactions with CF_3CH_2X (X = Br, I, OTf, OTs, NH_2) is based on cross-coupling reactions. However, due to the less impact on transition metal-catalyzed trifluoroethylation than trifluoromethylation through C–H activation under similar reaction condition, the development and use of novel trifluoroethyl group containing reagent is highly required.[4,6,8] On the other hand, hypervalent iodonium salts are considered as promising efficient reagents for carbon–carbon bond and carbon–heteroatom bond formation owing to its electrophilicity, longer shelf life and nontoxicity.[1,4,7,8] The Novak group recently reported 2,2,2-trifluoroethylation of indoles[1] and anilides[3] with 2,2,2-trifluoroethyl(mesityl)-iodonium triflate salt (Figure 3.1, **A**). The Shi group developed selective trifluoroethylation at C4-position with a salt **A**. The Zhang and Loh group reported palladium-catalyzed trifluoroethylation of aryl boronic acids and aromatic amides using salt A, respectively.[4,7]

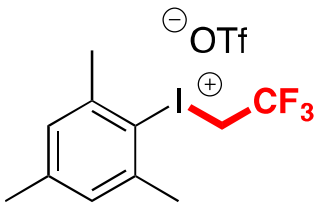


Figure 3.1. A representative iodonium salt for 2,2,2-trifluoroethylation

Quinazolinone derivatives are widely found in natural products, for example, luotonin A from *Peganum nigellastrum* and 2-methyl-4(3*H*)-quinazolinone from *Bacillus cereus* (Figure 3.2). In addition, derivatives show biological and pharmacological activities such as antitumor, anti-HIV, anti-inflammatory and antibacterial.[9-13] Owing to the properties of quinazolinone derivatives, they have been developed as interesting structural scaffold and many methodologies have constructed. However, to the best of our knowledge, there is no example of constructing metal-free *O*–trifluoroethylation with trifluoroethyl group containing hypervalent iodonium salt. Herein, we report late-stage metal-free *O*–trifluoroethylation of various quinazolinone derivatives with moderate to excellent yields.

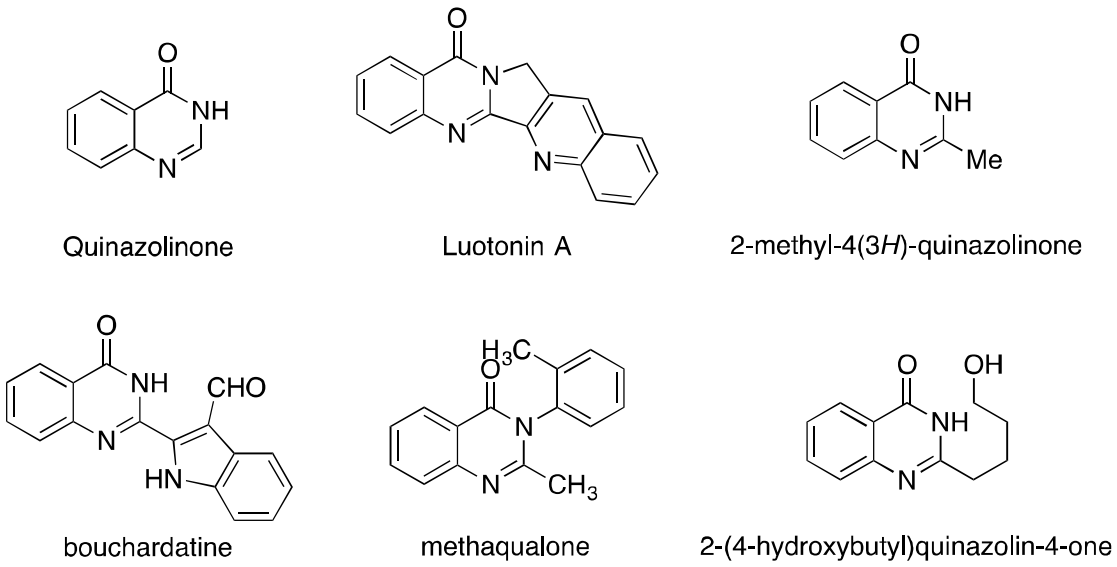
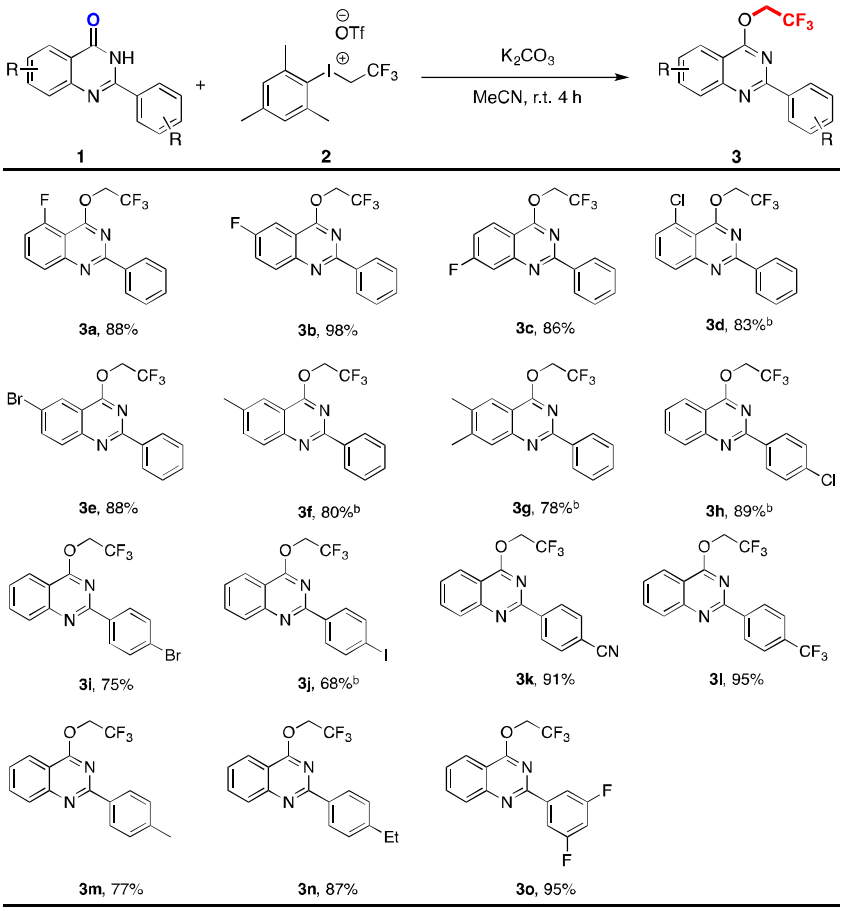


Figure 3.2. Quinazolinone and representative derivatives found in natural products

2. Results and Discussions

A Variety of quinazolinone derivatives (1a–1o) were examined to react site–selective *O*–trifluoroethylation (Table 3.1). Most of reactions completed within 4 hours whereas a few substrates required additional **2**, K_2CO_3 and reaction time to fully consume the starting materials (Table 3.1 entries d, f, g, h, j). To see the effect of substituent position on left side ring, we investigated *O*–trifluoroethylation of fluorine substituted arenes (Table 3.1, entries a–c). All substrates showed excellent yields and other halogen atom and methyl group substituted arenes showed good yields (Table 3.1, entries d–g). Substituents on right side ring effect were also examined (Table 3.1, h–o) and they showed moderate to excellent yields. In the case of halogen substituted substrates (Table 3.1, h–j), the yield tends to decrease as the atom becomes bulkier and less electronegative.

Table 3.1. *O*–trifluoroethylation of substituted quinazolinone derivatives



[a] Reaction conditions: **1** (50 mg), **2** (1.5 equiv.), K_2CO_3 (1.0 equiv.) MeCN (2 mL), r.t. 4 h. [b] **2** (2.0 equiv.), K_2CO_3 (1.5 equiv.), 24 h; Isolated yield.

3. Conclusion

In summary, we have demonstrated metal-free and site-selective *O*–trifluoroethylation of various quinazolinone derivatives using a hypervalent iodonium salt in mild condition. To confirm the organic molecules, ^{1}H, ^{13}C, ^{19}F NMR and HRMS were used. To see the generality of reaction, *O*-trifluoroethylation of substituted arenes on left or right side (a–g vs. h–o) and the position of substituents on arene were conducted and they did not affect the yield of desired product. Therefore, we believe that this late-stage *O*–trifluoroethylation of quinazolinones can be applied to medicinal field for diversification.

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